Effects of melatonin and SkQ1 long-term treatment during aging and development AMD-like retinopathy

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Melatonin and antioxidant SkQ1 act like mitochondria-targeted antioxidants.

Melatonin scavenged free radicals generated in the mitochondria, to reduce electron leakage from the respiratory complexes and to improve ATP synthesis, maintains reduced glutathione levels within the mitochondria thereby enhancing the antioxidative potential.

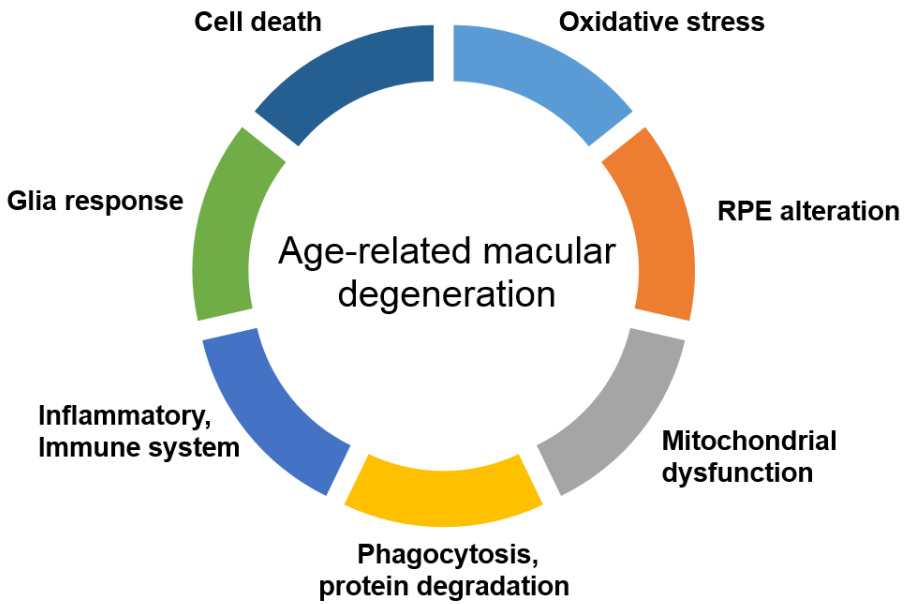
SkQ1 (10-(6-plastoquinonyl) decyltriphenyl-phosphonium) is plastoquinol derivative modified by a lipophilic cation then accumulate in the mitochondrial matrix and modulate of mitochondrial superoxide formation at specific sites of Complex I and III.

Detailed effects of melatonin and SkQ1 on the biochemical mechanisms underlying therapeutic effect of these drug during retinal aging and AMD progression remain unclear.

Here, we analyzed the effects of melatonin and SkQ1 long-term treatment during aging and development AMD using by animal model (OXYS rats).

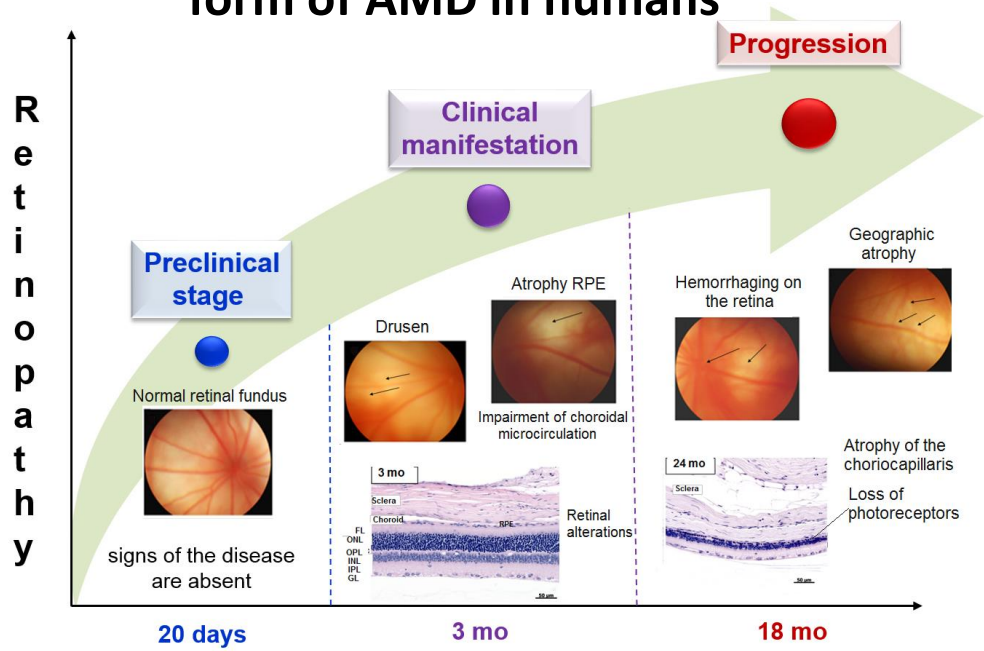
Summary, our data indicated that long-term treatment of melatonin and mitochondria-targeted antioxidant SkQ1 may be the different effects on molecular events resulting from different in genotype and environment.

Age-related macular degeneration (AMD) is the leading cause of blindness



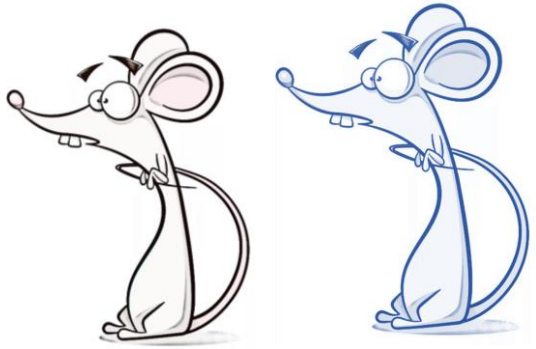
AMD is the predominant cause of visual loss in the macula in old people and is characterized by degeneration of retinal pigment epithelium and photoreceptors, impaired autophagy, DNA damage, mitochondrial dysfunction, increased levels of ROS and impaired of blood vessels. It is important that AMD is characterized by retina alterations similar to normal retinal aging. This fact complicates the study of AMD pathogenesis and the search for new therapy drugs.

OXYS rat's retinopathy corresponds to the dry atrophic form of AMD in humans



OXYS rats spontaneously develop a phenotype similar to human age-related disorders including AMD-like retinopathy. The clinical signs of AMD-like retinopathy appear by the age of 3 months. Significant pathological changes detected at the age of 12 months and manifest themselves as excessive accumulation of lipofuscin and amyloid in the RPE regions, disturbances in the morphology of the RPE sheet, including an increase in the proportion of multinucleated cells, hypertrophy, distortion of cell shape, and reactive gliosis.
Telegina et al; 2015-2019;
Kozhevnikova et a; 2013-2019;
Kolosova et al; 2002-2020

12-months- old
Wistar (control) and OXYS rats



12 months

Preliminary ophthalmoscopic examination showed that there was no difference between 12-month-old OXYS rats assigned to experimental and control groups.

Control diet
N=10

250 nmol/kg of SkQ1 per day
N=10

0.04 mg/kg of melatonin per day
N=10

Here, we observed similar effects of melatonin and SkQ1 in the retina of OXYS rats. Both SkQ1 and melatonin decreased the incidence and severity of retinopathy in OXYS rats.

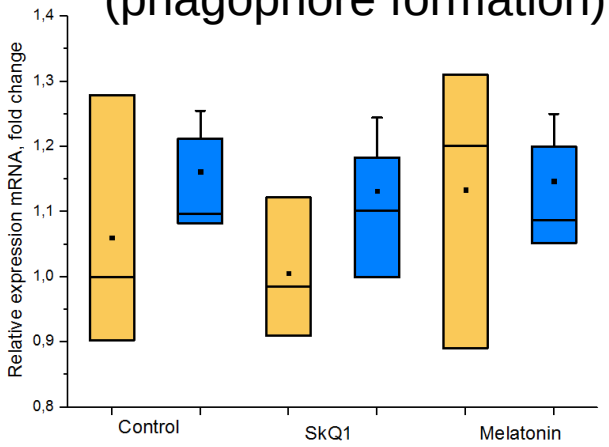
from the age of 12 to 18 months

18 months

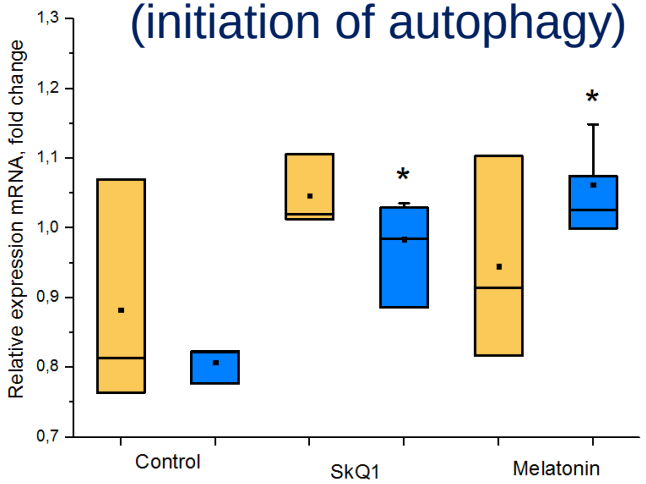
By the age of 18 months, retinopathy in control OXYS rats progressed. Both SkQ1 and melatonin decreased the incidence and severity of retinopathy in OXYS rats and did not influence on Wistar rats.

Effects of melatonin and SkQ1 long-term treatment on autophagy-related genes: increased mRNA level of *Beclin1* in OXYS rats after SkQ1 and melatonin treatment

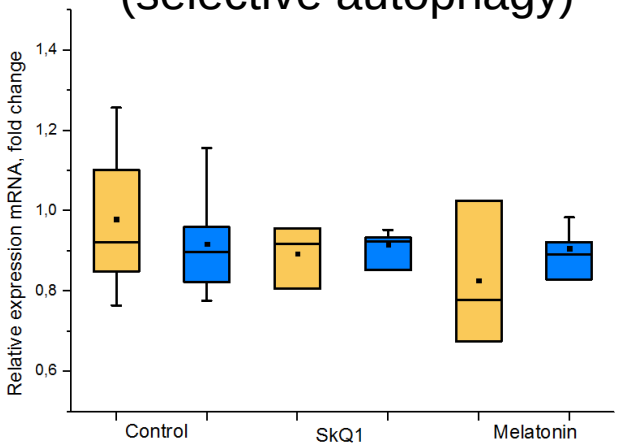
Atg7 (phagophore formation)

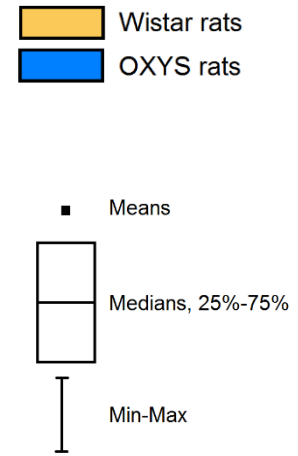


Beclin1 (initiation of autophagy)



Nbr (selective autophagy)

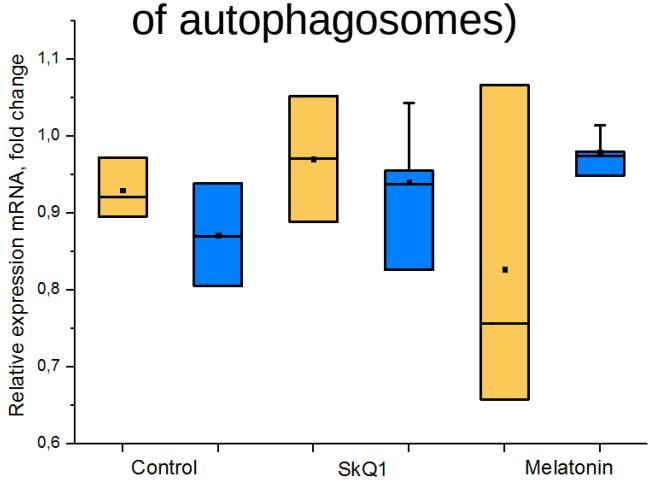




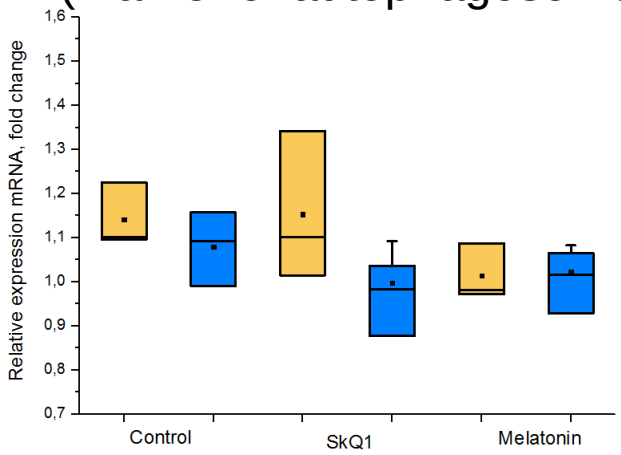
*significant differences from control animals of the same strain.

Nonparametric Kruskal–Wallis ANOVA we used.

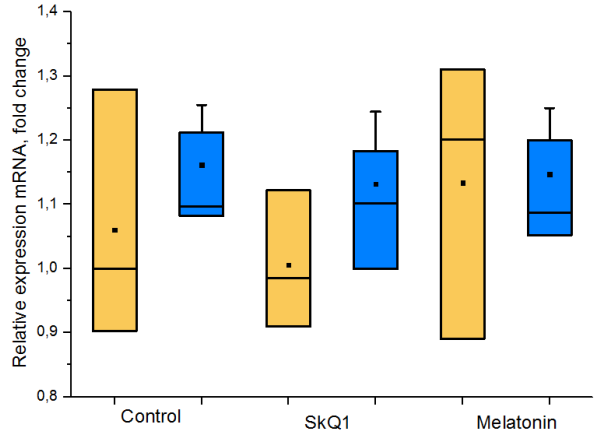
Gabarpl1 (elongation and maturation of autophagosomes)



Map1lc3b (marker of autophagosomes)

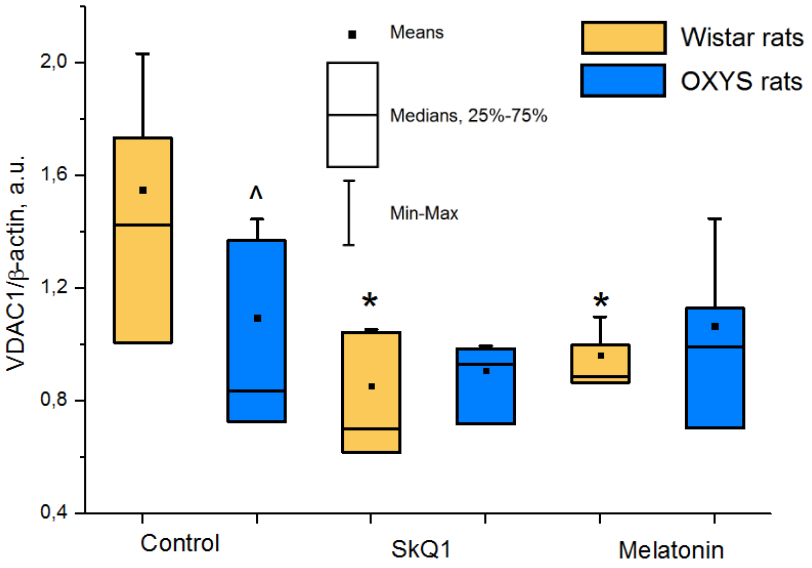


p62/Sqstm1 (link ubiquitinated proteins)

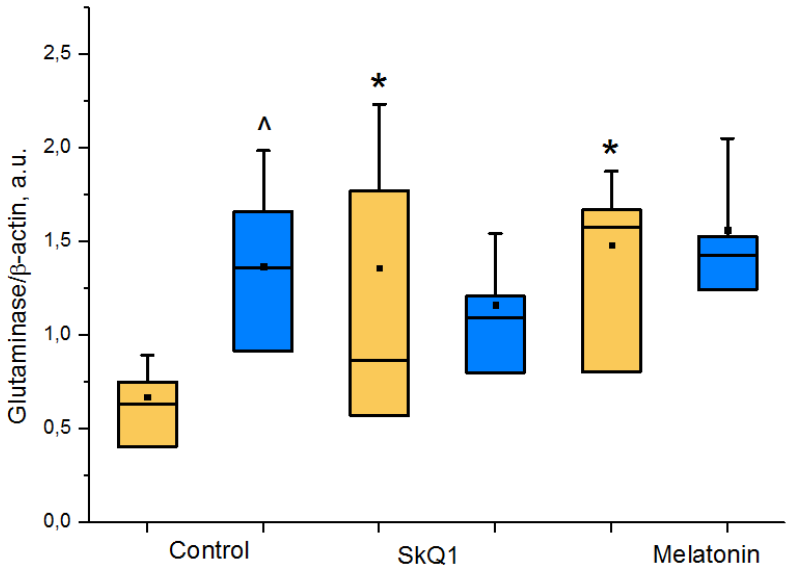


Similar effects of melatonin and SkQ1 in the retina

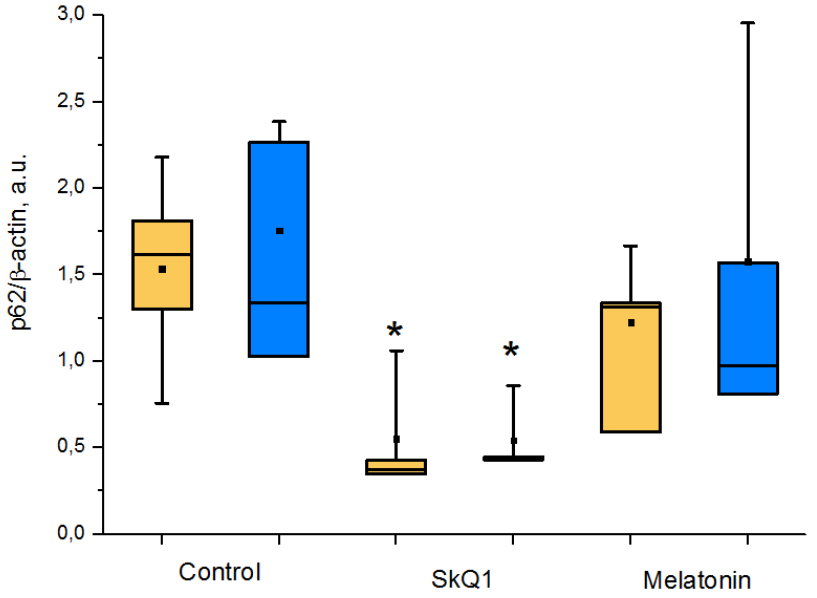
Treatment of melatonin and SkQ1 decreased VDAC1 level in Wistar rats and no influence on OXYS rats.



Treatment of melatonin and SkQ1 increased protein level of glutaminase in Wistar rat's retina.



Treatment of SkQ1 dramatically decreased p62/SQSTM1 protein levels in both OXYS and Wistar rats.



^Significant differences between the strains; *significant differences from control animals of the same strain. Nonparametric Kruskal–Wallis ANOVA we used.

VDAC1, also known as mitochondrial porin, associate with NADH oxidation and thus plays a role in cellular redox mechanisms.

In mammalian cells, glutamine is converted to glutamate by glutaminase (GLS), which functions as the rate-limiting enzyme, and then to α-ketoglutarate (α-KG).

p62/SQSTM1 is a scaffold protein for many signaling pathways, such as autophagy, apoptosis and inflammatory.

Thus, using Wistar rats with normal aging process and senescence-accelerated OXYS rats, which spontaneously develop AMD-like retinopathy, we demonstrated that long-term treatment of melatonin and mitochondria-targeted antioxidant SkQ1 may retard an age-related decline in the adaptability of retinal cells and may be considered as a strategy to slow down AMD.